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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/872,527	Guo et al.
Examiner	**Group Art Unit**
Thomas Cunningham	1644

Responsive to communication(s) filed on _____ .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-22 and 33-48* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-22 and 33-48* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

X See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *2, 4*

Interview Summary, PTO-413

X Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Applicant's election without traverse of Group I, claims 1-22 and 33-48 in Paper No. 5 is acknowledged. Applicant has elected bispecific monoclonal antibodies as a species of bridge molecule. Such a species is indicated as being encompassed by claims 1-22 and 33-48. Applicant has further elected the method exemplified in Example 6.6 and Figs 5 and 6. These examples encompass use of CD28:gp55 bispecific monoclonal antibodies.

2. The correction of the specification is acknowledged and does not raise the issue of new matter. It is presumed that Nature Medicine 4:1-5 (April 1997) does not refer to an article by Guo et al. and that the change is merely a correction of a typographical error. Verification of this presumption is required.

3. Claims 1-22 and 33-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compositions and methods of Example 6.6, does not reasonably provide enablement for other materially different CD28:gp55 bispecific antibodies, treatment of cancer cells not comprising gp55, treatment of cancer cells not comprising receptors for IFN-gamma or TNF.

Different monoclonal antibodies would be expected to bind to distinct epitopes of CD28 or gp55 and induce functionally distinct responses. For instance, a monoclonal antibody that binds to a portion of CD28 not involved in coactivation would not be expected to coactivate anti-tumor T cells.

Tumor cells which lack the gp55 determinant would not be targeted by antibodies which bind to gp55. Methods of using bispecific antibodies comprising determinants which bind to gp55 would not be expected to target and destroy tumor cells comprising non-gp55 antigens.

Tumor cells that do not express receptors for IFN-gamma or TNF would not be expected to react to the presence of these mediators. Paul indicates that cytokines must bind to specific cellular receptors in order to exert a biological effect.

4. Claims 1-22 and 33-48 to the extent that they embrace all the parameters of Example 6.6 are enabled for treatment of mice bearing hepa 1-6 tumor cells. Applicant has defined the elected species in accordance with the parameters of Example 6.6.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-22 and 33-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over admissions in the specification, Li et al., J. Immunol. 153:421 (1994), Renner et al., Science 264:833 (1994) or Krummel et al., J. Exp. Med. 182 459-465 (1995), in view of Paul, Fundamental Immunology (1993) and Darlington et al., JNCL 64:809 (1980).

The claims are directed to products and methods of using products such as bispecific monoclonal antibodies (Bi-MAbs) comprising a determinant that binds to CD28 and a determinant that binds to a tumor-associated antigen such as gp55.

The specification admits that it was known how to make bispecific antibodies, see e.g. page 33, lines 4-7.

McGowan et al. teach that stimulation of T cells via ligands that bind to CD28 on T cells induce cell-mediated responses that amplify both CD4+ and CD8+ T cell responses, see abstract.

Renner et al. teach that bispecific monoclonal antibodies to bind to tumor-associated antigens (CD30) and to either CD3 or CD28 "target human T cells to the tumor cells in vivo". Page 833 teaches preactivation of T cells using interleukin 2 and antibody to CD3.

Krummel et al. teach that antibody engagement of CD28 on T cells augments T cell responses and can supply costimulation to T cells encountering APCs deficient in costimulation (Hepa 1-6 cells are deficient in antigen presentation because they lack MHC Class I expression, see pages 29-30 of the specification).

Paul, Fundamental Immunology teaches the activities of IFN-gamma and TNF.

The primary references do not teach antigens, like gp55, from hepatoma cells such as HePa 1-6.

Darlington et al. teach hepatoma cells, see also page 29 of the specification.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to make bispecific antibodies comprising determinants that bind to CD28 on T cells and determinants that bind to antigens on tumor cells, such as gp55 on HePa 1-6 cells for the purpose of targeting T cells to hepatoma cells via a bridging antibody, that would bind to both T cells and tumor cells. Further, based on the teachings of the primary references one with ordinary skill in the art would expect that such bispecific antibodies would provide costimulation to CTLs and thus enhance antitumor CTL activity. The addition of IFN-gamma and TNF would be expected to provide activation of antigen presenting cells like macrophages, augment T cell responses and other cellular responses such as increases in neutrophil adhesion useful for targeting or destroying tumor cells.

While the cited art may not teach the specific hepatoma antigen, gp55, there does not appear to be anything unique about this antigen to distinguish it from hepatoma antigens in general. The critical characteristic of hepatoma antigens is that they are expressed as targets by hepatoma cells to permit binding of an CD28 specific product.

8. Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 305-7401. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[tom.cunningham@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D., J.D., whose telephone number is (703) 308-3968. Dr. Cunningham can generally be reached Monday through Thursday from 7:30AM to 6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800